984877

PATENT SPECIFICATION

NO DRAWINGS

984.877

Date of Application and filing Complete Specification **Aug. 15, 1963.**

No. 32231/63.

Application made in Germany (No. Z9592 IVd/12p) on **Aug. 16, 1962.**

Complete Specification Published March 3, 1965.

Index at acceptance: —C2 C(1E3K1, 1E3K4, 1E7C1, 1E7D1, 1E7F1, 1E7H1, 1E742, 1E7L, 1E7N5, 1E7P1, 1F2A1, 1F2C2, 1F2D3, 1F2E)

Int. Cl.:—**C 07 d**

COMPLETE SPECIFICATION

Improvements in and relating to 6-halonucleosides

We, ZELLSTOFFFABRIK WALDHOF, of 176, Sandhofer Strasse, Mannheim-Waldhof, Germany, a Joint Stock Company organised under the laws of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 6-halo-nucleosides and, more particularly, to a process for the preparation of 6-halo-nucleosides.

In the preparation of 6-chloro-nucleosides the starting substance has hitherto been the mercury salt of the corresponding 6-chloropurine body which has been reacted with 1 - chloro - 2, 3, 5 - tribenzoyl - β - D - ribofuranose. This method, however, is troublesome and there are considerable losses.

It has now been found that 6-halo-nucleosides, the sugar residues of which are completely esterified, especially 6-chloro-nucleosides are obtained in a simple and quick way and with good yields and a high degree of purity when 6-mercapto-nucleosides, the sugar residues of which are completely esterified, are reacted, in solution or suspension, with halogens.

Suitable starting substances for the process according to the invention are purines substituted in the 6-position by mercapto groups and having a sugar residue in the 9-position. These purines may be further substituted by mercapto groups in the 2, and/or 8-positions. Examples of such starting substances include 6 - mercapto - 9 - (2^1, 3^1, 5^1 - tribenzoyl) - β - D - ribofuranosylpurine, 2 - amino - 6 - mercapto - 9 - (2^1, 3^1, 5^1 - tribenzoyl) - β - D - ribofuranosylpurine, 2 - amino - 6 - mercapto - 8 - bromo - 9 - (2^1, 3^1, 5^1 - tribenzoyl) - β - D - ribofuranosylpurine, 2 - hydroxy - 6 - mercapto - 9 - (2^1, 3^1, 5^1 - tribenzoyl) - β - D - ribofuranosylpurine, 2, 6 - dimercapto - 9 - (2^1, 3^1, 5^1 - tribenzoyl) - β - D - ribofuranosylpurine, 2 - amino - 6 - mercapto - 9 - (2^1, 3^1, 5^1 - triacetyl) - β - D - ribofuranosylpurine, also pyrimidine derivatives which are substituted by a mercapto group in the 6-position, such as 2 - oxo - 6 - mercapto - 3 - (2^1, 3^1, 5^1 - tribenzoyl) - β -D - ribofuranosylpyrimidine, 2 - oxo - 5 - bromo - 6 - mercapto - 3 - (2^1, 3^1, 5^1 - tribenzoyl) - β - D - ribofuranosylpyrimidine, 2 - oxo - 6 - mercapto - 3 - (2^1, 3^1, 5^1 - triacetyl) - β - D - ribofuranosylpyrimidine.

Where the nucleosides to be used as starting substances are substituted in the 2 and/or 8-position by mercapto groups these groups are replaced by halogen during the process according to the present invention.

The 6-mercapto-nucleosides used as starting substances are known or can be prepared by analogous processes to those used by preparing the known compounds. According to one method they are prepared by reacting a 6-hydroxy-nucleoside with phosphorus pentasulphide (P_2S_5).

The 6-mercapto-nucleosides are dissolved or suspended in inert organic, preferably anhydrous, solvents. The most important of such solvents are alcohols such as methanol, ethanol or butanol, chloroform, carbon tetrachloride, benzene, toluene, or mixtures with or among the above mentioned solvents.

The solution or suspension of the 6-mercapto-nucleosides is suitably cooled to temperatures below 35° C., preferably between +10° and —10° C. Into this solution or suspension halogen is either passed in as a gas or added as a liquid, if necessary in solution. Constant movement of the reaction solution ensures that during the reaction the temperature does not rise appreciably. After addition of the amount of halogen required for

[*Price* 4*s.* 6*d.*]

the reaction, the reaction mixture is poured into ice water, and the halogen derivatives is thereby precipitated. The residue is dissolved in ether and after drying this solution, the ether is evaporated and if desired the 6-halo-nucleoside is recrystallised from suitable agents.

The exchange of a mercapto group with a halogen atom is known in the case of purines. It was surprising, however, that this process can also be used with nucleosides, the sugar residue of which is completely esterified, since a partial splitting off of the ester groups or of the sugar residue was anticipated. Owing to the high degree of purity of the 6-halo-nucleosides obtained by the process according to the present invention, they are suitable for further reactions, e.g. to the 6-amino-nucleosides, without additional steps.

The process according to the invention is illustrated in more detail by means of the following examples:

EXAMPLE 1

2.2 g of 6-mercapto-9-(2^1,3^1,5^1-tribenzoyl)-β-D-ribofuranosylpurine were dissolved in 30 to 40 ml of absolute methanol and cooled to 0°. Gaseous chlorine was passed in for 10 to 15 minutes at this temperature with intensive stirring. The solution was then poured on to about 100 ml. of ice water. The precipitated 6 - chloro - 9 - (2^1, 3^1 5^1 - tri - benzoyl) - β - D - ribofuranosyl - purine was separated. After treatment of the residue with ether in the hot, the undissolved material was filtered off, and the ether solution dried over sodium sulphate and the ether evaporated in vacuo. The residue was recrystallised from isopropanol and was found to be indentical in its chemical and physical properties with the 6 - chloro - 9 - (2^1, 3^1, 5^1 - tribenzoyl) - β - D - ribofuranosyl - purine prepared by the method of Kissman and Weiss (J. Org. Chem., 1956, *21*, 1053). Yield: 1.2 g=54.5% of theory.

EXAMPLE 2

1 g of 2 - amino - 6 - mercapto - 9 - (2^1, 3^1, 5^1 - tribenzoyl) - β - D - ribofuranosyl - purine was suspended in 20 ml. of carbon tetrachloride dried over P_2O_5 and cooled externally with an ice bath to about +10° C. Gaseous chlorine was passed in for 35 minutes at this temperature, with stirring. The chlorinated product was then filtered off by suction, washed with carbon tetrachloride and then dried in vacuo. The 2 - amino - 6 - chloro - 9 (2^1, 3^1, 5^1 - tribenzoyl) - β - D - ribofuranosyl - purine obtained was recrystallised from dioxan-water. Yield: 0.6 g.= 59.8% of theory.

EXAMPLE 3

1 g. of 2 - amino - 6 - mercapto - 8 - bromo - 9 - (2^1, 3^1, 5^1 - tribenzoyl) β - D - ribofuranosyl - purine was dissolved in absolute propanol and cooled to about —20° C. by means of a freezing mixture. Gaseous chlorine was then passed in for 20 to 30 minutes at this temperature. The reaction mixture was freed from excess chlorine by a stream of air and poured on to about 100 g. of crushed ice. The 2 - amino - 6 - chloro - 8 - 9 - (2^1, 3^1, 5^1 - tribenzoyl) β - D - ribofuranosyl - purine which precipitated was filtered off by suction and purified as indicated in Example 2. Yield: 0.7 g=69.7% of theory.

WHAT WE CLAIM IS:—

1. Process for the preparation of 6-halo-nucleosides, the sugar residues of which are completely esterified, in which 6-mercapto-nucleosides, the sugar residues of which are completely esterified, are reacted with halogen in a solution or suspension in an inert organic solvent or suspension means.

2. Process according to claim 1, in which the halogenation is effected in alcoholic, preferably methanolic solution.

3. Process according to any preceding claim in which the halogenation is carried out at temperatures below 35° C.

4. Process as claimed in claim 3 in which the temperature lies in the range 10° to —10° C.

5. Process for the preparation of 6-halo-nucleosides substantially as hereinbefore described with reference to any one of the examples.

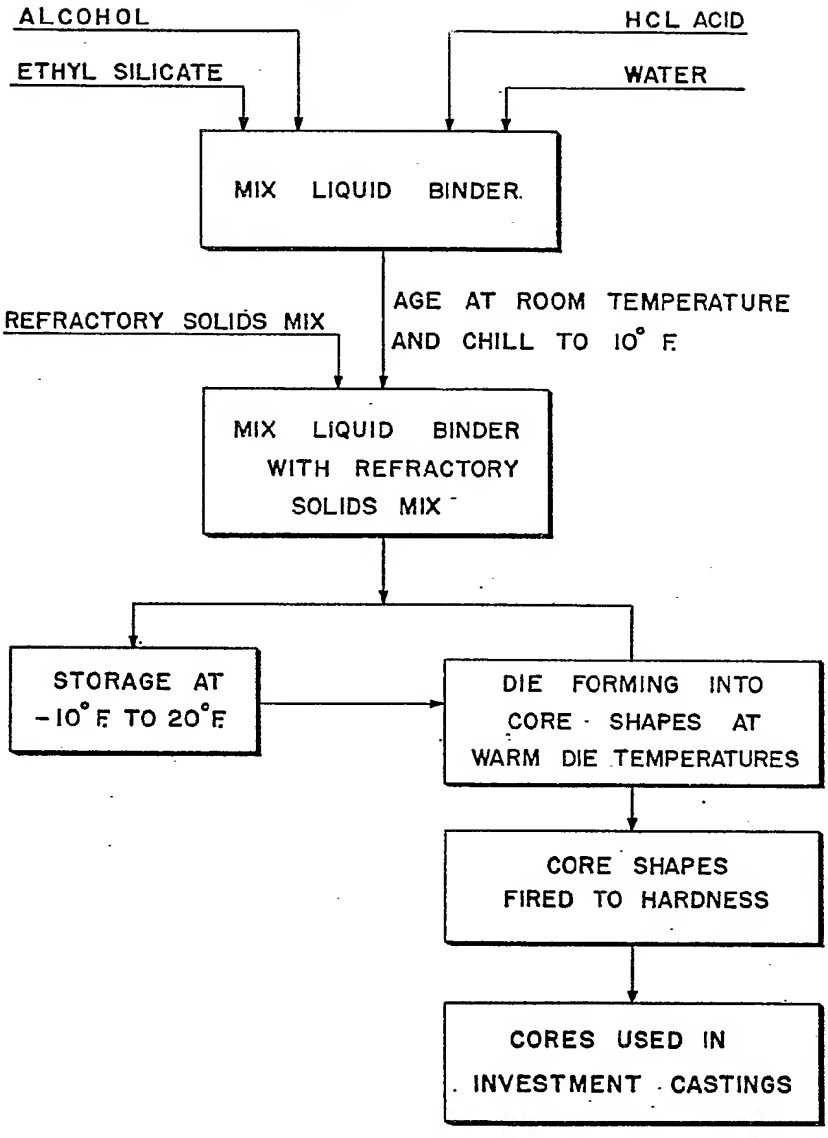
6. 6-halo-nucleosides whenever produced by the process of any preceding claim.

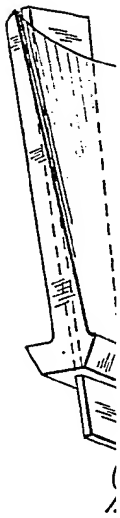
W. P. THOMPSON & CO.,
12, Church Street,
Liverpool, 1.
Chartered Patent Agents.

Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to Patent No. 924246.

Leamington Spa: Printed for Her Majesty's Stationery Office by the Courier Press.—1965.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

FIG. 1


ALCOHOL
ETHYL SILICATE
HCL ACID
WATER
MIX LIQUID BINDER.
AGE AT ROOM TEMPERATURE AND CHILL TO 10° F.
REFRACTORY SOLIDS MIX
MIX LIQUID BINDER WITH REFRACTORY SOLIDS MIX
STORAGE AT -10° F. TO 20° F.
DIE FORMING INTO CORE SHAPES AT WARM DIE TEMPERATURES
CORE SHAPES FIRED TO HARDNESS
CORES USED IN INVESTMENT CASTINGS



19

984887 COMPLETE SPECIFICATION
2 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheet 1

CID

—

ATURE

NTO
AT
ATURES

S
IESS

N
TINGS

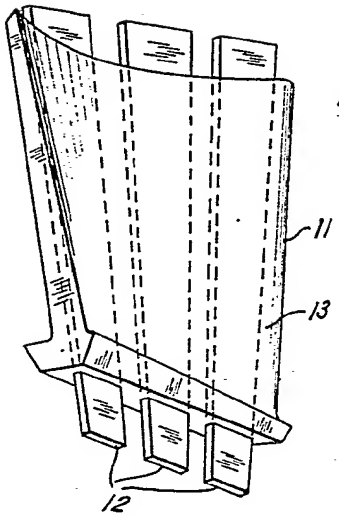


FIG. 2

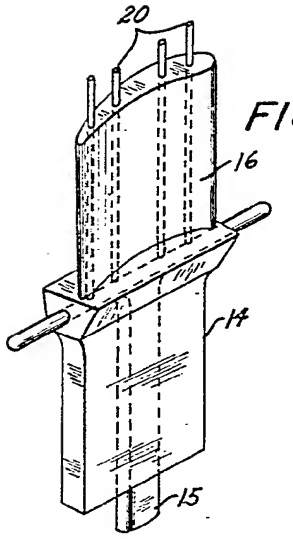


FIG. 3

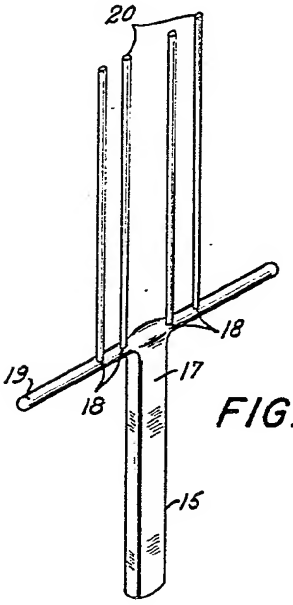
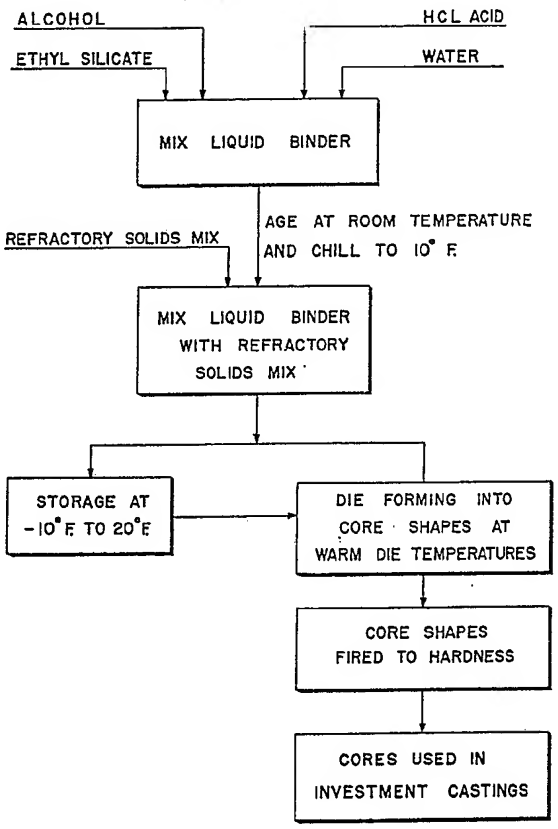


FIG. 4

984887 COMPLETE SPECIFICATION
2 SHEETS This drawing is a reproduction of the Original on a reduced scale
Sheet 1

FIG. 1



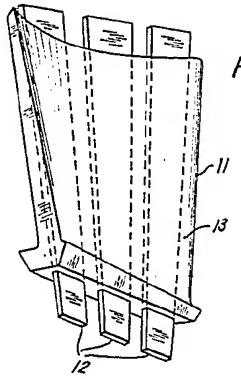


FIG. 2

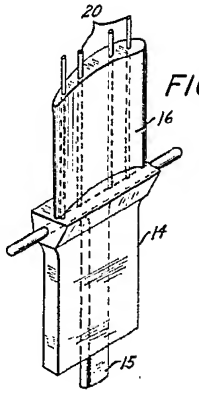


FIG. 3

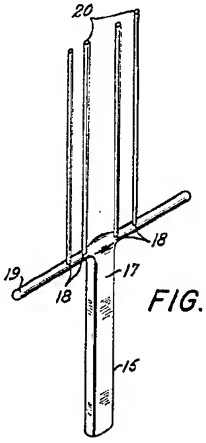
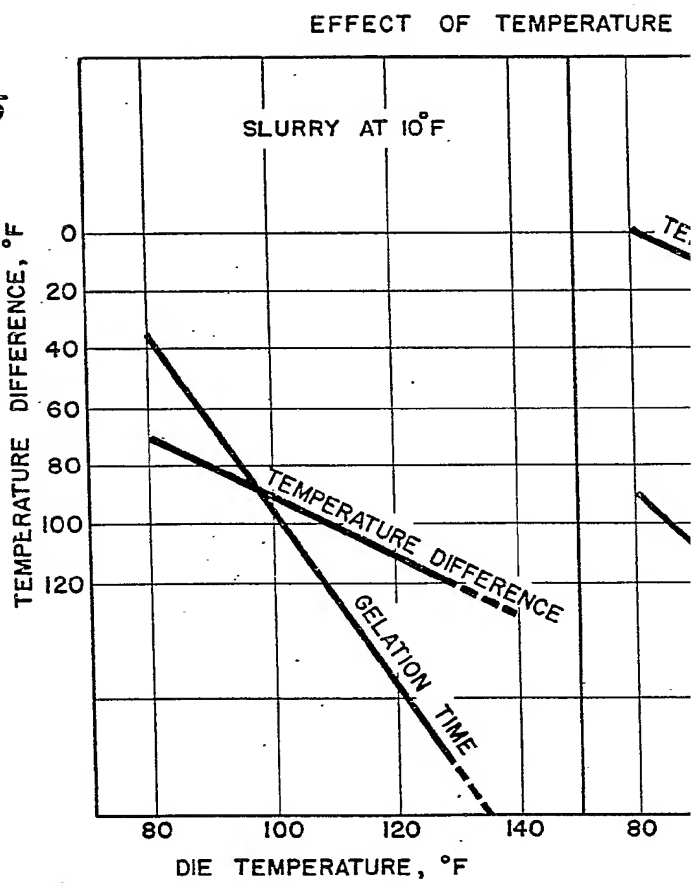


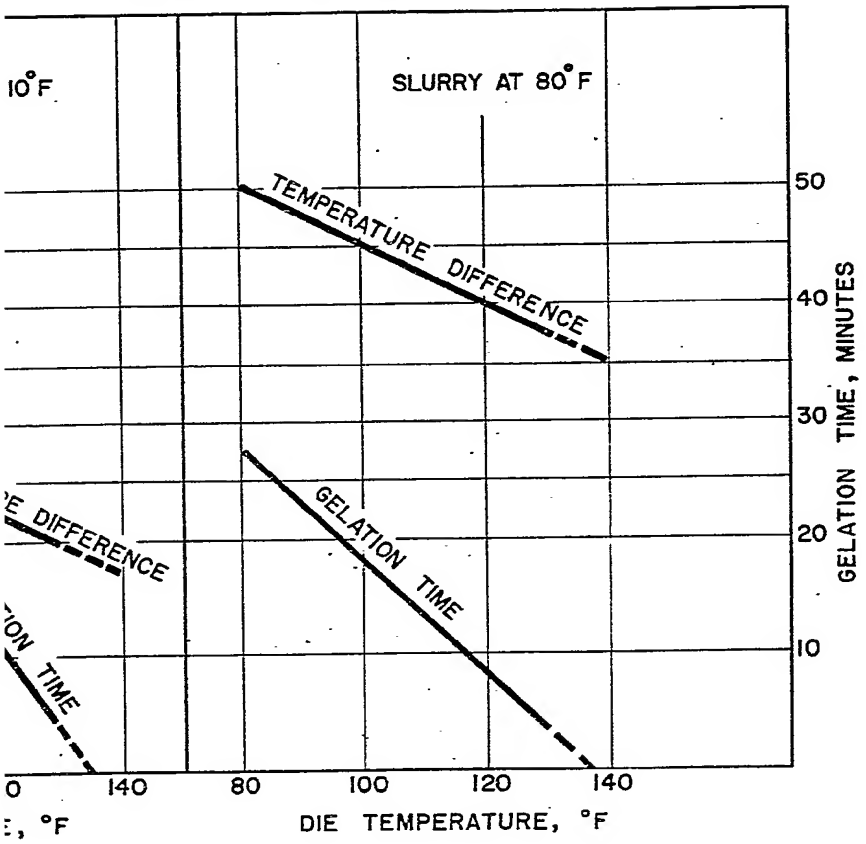
FIG. 4

FIG. 5


EFFECT OF TEMPERATURE
SLURRY AT 10°F
TEMPERATURE DIFFERENCE, °F
0
20
40
60
80
100
120
TEMPERATURE DIFFERENCE
GELATION TIME
80
100
120
140
80
DIE TEMPERATURE, °F

984887 COMPLETE SPECIFICATION
2 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheet 2

T OF TEMPERATURE ON GELATION TIME



984887 COMPLETE SPECIFICATION
2 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheet 2

FIG. 5